1-Chloro-4-(trifluoromethyl)benzene

NIEHS nominated 1-Chloro-4-(trifluoromethyl)benzene (PCBTF, or p-chlorobenzotrifluoride) for toxicological characterization due to changes in industrial and consumer use and an unknown chronic toxicity profile.

PCBTF is primarily used as a solvent in commercial surface finishes in addition to being both a solvent and intermediate in a range of organic reactions. Exemption from volatile organic compound (VOC) regulations has led to an increase in the use of PCBTF as a replacement for other solvents in a variety of commercially-available paints and other finishes. NIEHS notes that use of PCBTF in such consumer products, or more importantly their improper use or disposal, may lead to an increase in public exposure outside of occupational contexts, although there is no information available to either support or estimate this potential increase in exposures.

PCBTF is no longer produced domestically, and the amount of PCBTF used in the United States has declined significantly in spite of its VOC exemption. EPA records show PCBTF usage in the 10-50 million pound range in 1986, 1990, 1994 and 1998, but that figure dropped to the 1-10 million pound range in 2002 and 2006.

Originally nominated to NTP in 1981, NIEHS notes in its current Chemical Information Profile that PCBTF has been the subject of a range of toxicity assays in several species of animals that evaluated acute toxicity, subchronic toxicity, pharmacokinetics, developmental toxicity, carcinogenicity, genotoxicity, and neurotoxicity endpoints and investigated structure-activity relationships, histopathology and metabolic interactions. In the immediate vicinity of former manufacturing sites, PCBTF contamination during active periods of manufacture was measured in residents (less than 1 ppm in exhaled breath), fish (0.17—2 ppm) and air (3 ppb) at significantly lower concentrations than have demonstrable toxic effects *in vivo* and *in vitro*. In a 13-week inhalational study in rats, there were no changes seen in any measured clinical chemistry parameter at doses up to 252 ppm outside of an increase in relative liver weights between dose groups. Additionally, there were no adverse observations recorded either during the exposures or during detailed weekly clinical evaluations (Newton et al. 1998). Subchronic studies report an absence of pre-cancerous hematological changes or other histopathological indications of carcinogenicity.

PCBTF has a relatively brief half-life in both the body and the environment. Except for the fraction that is more slowly removed from fatty tissues, PCBTF is largely eliminated from the brain, kidney, liver, lungs, muscle and blood within 24 hours of administration (Newton et al. 1998; NTP 1991). Excluding a continuous source of PCBTF exposure, bodily concentrations decay significantly (more than 80 percent) during this post-exposure period. Spilled into water, PCBTF volatilizes readily in a matter of hours. In open containers, PCBTF evaporates and is degraded in the atmosphere on the order of two months, which is a primary characteristic that has kept it exempt from VOC regulations (Maul et al. 1999). Bioconcentration is an unlikely concern relative to federally established thresholds (Maul et al. 1999). These studies have shown that PCBTF is quickly eliminated from most tissues in the body and causes few adverse effects over a wide dose range, and for these reasons it has not been deemed a significant public health hazard.

Though there is little chronic toxicity data specifically prepared for PCBTF, there is a broad range of other toxicological information that suggests PCBTF has a low enough risk profile that such information is not essential to mitigating the risk of exposure relative to chronic toxicity effects. NIEHS addresses clinical measures of toxicity that it considers sufficient cause for additional toxicity testing, but in many instances the cited effects only occur at megadose ranges. NIEHS

notes, for instance, that subchronic inhalational and oral exposure in rats produces clinical signs of toxicity that include salivation, tremors, altered hematological and hepatocellular profiles. These signs, however, were only noted at 1000 mg/kg/day, which is greatly outside of the range expected in a potential spill of PCBTF-containing paint products. PCBTF has low subchronic oral toxicity as well, and neither pathological nor adverse biochemical effects were found at doses up to 10 mg/kg/day, which has been described as PCBTF's no-observable-effect level (Macri et al. 1987). The same study demonstrated that PCBTF never produces severe effects in rats, leading to the conclusion that PCBTF "does not seem to be a chemical of great concern in public health." Observations of hyaline droplet nephropathy and liver hypertrophy as well are noted at only the highest doses measured in oral toxicity tests, 1000 mg/kg/day, and not at any of the lower dose levels. "Of the histological changes observed," the study authors note, "the consistent picture of hyaline droplet nephrosis and increased relative kidney weights in males in the 1000 mg/kg group was the only change clearly attributable to [PCBTF]" (Macri et al. 1987). For occupational exposures, an 8-hour time-weighted average (TWA) permissible exposure level was suggested at 25 ppm based on results from another study, which is less restrictive than the 20 ppm 8-hour TWA established by Kowa American Corporation, the United States chemical importation company that renominated PCBTF (Newton et al. b, 1998; KOWA MSDS).

In spite of over thirty years of industrial use, very little data has been collected on the health effects in occupational settings where PCBTF has been produced or used. NIEHS references a single retrospective epidemiologic study of approximately 4,000 Niagara Plant workers that reported increased respiratory and stomach cancers (Rockette et al. 1983). This study, however, failed to adjust for confounding variables such as cigarette smoking in addition to an absence of chemical exposure measurements (NRC 2005). Considering that this plant used or manufactured manganese perchlorate and 23 other chemicals, such significant gaps in the study render the relationship of PCBTF exposure to any increase in standardized mortality ratios impossible to measure. This study does highlight the continued need for well-designed epidemiologic cohort studies within industries that have used PCBTF for decades. Regarding concerns that chronic low dose exposure to PCBTF may be carcinogenic among already-exposed populations, the conspicuous lack of human evidence has forced reliance on toxicological data from animal tests and this lack of epidemiologic data should be corrected immediately rather than resorting to yet more animal studies.

Related compounds have low hazard profiles generally (Knochel et all, 1999). PCBTF is structurally similar to other benzotrifluorides (BTFs), a group of relatively inert trifluoromethyl-substituted aromatic compounds used in similar applications as both solvents in reactions and in surface coatings. PCBTF also shares structural similarities with dichloromethane and benzene, both of which have well-characterized toxicological profiles and are much more toxic than BTFs. Benzotrifluoride (BTF) itself is less acutely toxic than both dichloromethane and benzene, both of which share functional groups with PCBTF and other BTFs, and its higher boiling point reduces the tendency toward evaporative loss and inhalational exposure. Both dichloromethane and benzene are more acutely toxic and cause more severe irritation to the eye and skin than BTFs, in addition to demonstrated reproductive and teratogenic effects following subchronic and chronic exposures (Maul et al. 1999). Though there is comparatively little chronic exposure data on PCBTF, results that have been collected "may suggest that [PCBTF] will not show the same chronic toxicity as [dichloromethane and benzene]" (Maul et al. 1999). Differences in the toxicological profiles of BTFs and these two chemicals suggest that PCBTF is generally less toxic, acutely and chronically, than either of these known carcinogens.

To summarize, there is virtually nothing known about possible consumer exposure to PCBTF, which is used less today than in the past in spite of its VOC exemption. While results of acute and

subchronic toxicity studies suggest that PCBTF has a low toxicity profile, there is little evidence to support the proposed approach to renewed chronic toxicity and carcinogenicity testing. Weak evidence for human carcinogenicity and the fact that existing recommendations for permissible exposure limits virtually remove potential human health risks strongly suggests that additional PCBTF testing should be assigned a low priority. Rapid environmental degradation and elimination from the body suggests that chronic public exposure outside of sources of continuous contamination is not a significant concern. Without further exploration of epidemiologic evidence linking occupational exposure to PCBTF with adverse health events, the proposed research program is premature. Structural considerations suggest that PCBTF would fail to produce clear evidence of adverse effects at doses relevant to human exposure in animal models. PCBTF is dissimilar enough from benzene and dichloromethane that the chronic toxicity profiles of the latter two compounds are not expected to represent PCBTF. Targeted epidemiological analysis is the only approach likely to reveal any toxicities resulting from chronic exposure in any context. This is particularly true considering the fact that consumer exposure is unlikely to result in exposures above levels already established as causing no observable biological effect. We recommend that the potential for human exposure be assessed accurately before any further development of this research program, and that epidemiologic studies of workers occupationally exposed during the last thirty years be initiated before additional *in vivo* testing is considered.

References

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